In re Application of: Yoram Reiter et al
Serial No.: 10/510,229
Filed: October 13, 2004
Office Action Mailing Date: January 24, 2007

Examiner: Lucas, Zachariah
Group Art Unit: 1648
Attorney Docket: 28429

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 141-160 are in this Application. Claims 141-160 have been rejected under 35 U.S.C. § 103. Claims 141, 144-160 have been rejected under 35 U.S.C. § 112. Claims 141, 150 and 151 have been amended herewith. New claims 196-211 have been added herewith.

35 U.S.C. § 112 Rejections

The Examiner has rejected claims 141 and 144-160 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for methods of using antibodies to kill or damage cells using the indicated antibodies where the antibody or fragment thereof is attached to a toxin, does not reasonably provide enablement for methods of killing cells merely through the exposure of the cells to the antibodies. In addition, the Examiner states that because the application also teaches that the antibodies are useful for the detection and purification of cells it thereby indicates that the antibodies themselves do not kill or damage cells. The Examiner's rejections are respectfully traversed. Claim 150 has been amended herewith. New claims 196-211 have now been added.

Applicants point out that it is well known in the art that antibodies having high affinity and binding specificities to their targets can be used for cell killing via the antibody constant region (Fc) which induces antibody-dependent cell mediated cytotoxicity (ADCC) or the complement cascade [see for example, Weir AN., et al., Biochem Soc Trans. 2002 Aug;30(4):512-6, Abstract, attached herewith]. In addition, in contrast to Examiner's assertion, the instant application provides sufficient guidance and direction for practicing cell killing using the antibodies of the instant application, all of which negate the need to attach a toxic moiety thereto. See for

example, the description on Pages 21 (lines 31-33), 22 (lines 1-3, 23-27), 26 (lines 31-33), 27 (lines 1-20), and 50 (lines 19-24) of the instant application as filed.

With respect to Examiner's assertion that because the application also teaches that the antibodies are useful for the detection and purification of cells it indicates that the antibodies themselves do not kill or damage the cells, Applicants point out that detection and purification of cells from *in vitro* constituents devoid of the complement system for example cannot result in cell killing. In addition, *in vivo* diagnostics is enabled using antibody fragments that lack the Fc region and therefore are unable to kill or damage the cells.

Thus, it is Applicants' strong position that one of ordinary skill in the art of immunology would be able to select the appropriate antibody composition to induce cell killing as claimed.

Notwithstanding the above, Applicants have elected to add new claims 196-198 pertaining to the use of antibody or antibody fragment which comprises an antibody constant region that is capable of inducing antibody-dependent cell mediated cytotoxicity (ADCC) or a complement cascade. Support for claims 196-198 can be found on Pages 27 (lines 7-20) and 50 (19-24) in the instant application as filed.

The Examiner has further rejected claim 150 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that the claim reads on a genus of methods comprising the use of an antibody or fragment thereof that binds to a human antigen-presenting molecule/antigen wherein the fragment comprises the sequence of SEQ ID NO:23, however, the application provides no demonstration that the presence of SEQ ID NO:23 in an antibody binding domain correlates with the antibody's ability to bind such a complex, thus the application has provided only a single working example of the claimed genus and not demonstrated any function/structure correlation with the required binding affinity. In addition, the Examiner states that the art relating to antibodies recognizes that the formation of an intact antigen-binding site generally

requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The Examiner's statements are respectfully traversed.

In order to expedite prosecution in this case, Applicants have elected to amend claim 150 and add new claims 199-211 to include the six CDRs (three of the heavy chain and three of the light chain) of specific antibodies of the claimed invention which were selected by their ability to bind the specific human complexes of antigen presenting molecules and the antigens derived from a pathogen. Support for amended claim 150 and new claims 199-211 can be found on Table 3, Pages 72-73 in the instant application as filed.

In view of the above claim amendments, arguments and remarks Applicants believe to have overcome the 35 U.S.C. § 112, first paragraph rejections.

35 U.S.C. § 103 Rejections

Reiter in view of Andersen

The Examiner has rejected claims 141-149, 151-155, 158 and 159 under 35 U.S.C. § 103(a) as being unpatentable over Reiter et al. (PNAS 94:4631-4636, 1997), further in view of the teachings of Andersen et al. (WO 97/02342). The Examiner states that Reiter et al. teach a method of killing a B-cell infected with a virus by contacting the cell with an antibody that binds to an MHC molecule complexed with an antigen of the virus except that the MHC-complexes targeted in the reference comprise murine and not human, MHC molecules. In addition, the Examiner states that while the reference does not actually kill such cells through administration of the conjugates to an individual, the reference does suggest that such conjugates may be used to develop therapeutic agents, albeit against cancer; and while the reference does not teach that the MHC in the targeted complex is a human MHC, the reference does suggest such embodiments. With respect to Andersen et al., the Examiner states that

Andersen et al. provide similar teachings to those of Reiter et al. and indicates that virus infections may also be targeted. The Examiner further states that it would have been obvious to have used antibodies that target any viral peptide/MHC complex, including those of either the H-K^k type as demonstrated in Reiter et al., or of other types including HLA-A2 and thus the combined teachings of these references render the claimed methods obvious.

The Examiner's statements are respectfully traversed.

Andersen et al. teach an antibody (Fab 13.4) directed against mouse MHC-peptide complexes and not against human MHC-peptide complexes and Reiter et al. (1997) teach using such an antibody (Fab 13.4) for killing mouse cells (L929, RMA-k) but does not provide the necessary teachings to arrive at methods of killing human cells infected with pathogens (using e.g., antibodies directed against human MHC-peptide complexes). Thus, Applicants point out that in sharp contrast to Examiner's assertion the teachings of Andersen et al. (1997) and/or Reiter et al. (1997) could not have resulted in antibodies against human MHC-peptide complexes which are suitable for human therapeutic applications.

Attached are two declarations under 37 CFR 1.132 by Prof. Charles DeLisi and Prof. Vincenzo Cerundolo, two world experts in the fields of immunochemistry and immunology, respectively, stating that the claimed invention satisfies a long-felt need which was recognized, persistent but not solved by others including by the teachings of Andersen et al., 1997 and Reiter et al., 1997.

The declarations are accompanied by peer reviewed documents showing that for more than 15 years prior to the filing date of the invention discussed and claimed in the above-identified patent application, research groups have all failed in generating T-cell receptor-like (TCRL) antibodies, let alone using them for killing virus infected human cells. Thus, Tamminen WL., et al., (Eur. J. Immunol. 1987, 17:999-1006; see, in particular, Abstract; attached herewith), failed to obtain antibodies against MHC-viral peptide complexes.

In addition, Rubin B., et al., 1989 (Res. Immunol. 140:67-74; attached herewith) tested more than 1500 antisera but could not find any antibodies specific for complexes of MHC-insulin peptide (see Page 71, middle paragraph in Rubin et al.).

Chames P., et al., (PNAS, 2000, 97:7969-7974, attached herewith; see in particular Page 7970, left column, first paragraph), states that although highly desired for therapeutic applications, selection of antibodies that recognize MHC-peptide complexes is a difficult task. Chames et al. attempted to identify an antibody with specificity against human MHC-peptide complex and identified one phage clone displaying Fab G8 which recognized HLA-A1-MAGE-A1 (a melanoma peptide) but not HLA-A1-MAGE-A3 complexes. However, when the soluble G8 Fab fragment, which was purified from the phage clone, was reacted with the target complex, the authors could not find conditions that eluted the antibody without also dissociating the β2m from the HLA-A1 heavy chain, thus, they failed to obtain a TCR-like antibody with specificity to human MHC-peptide complex (see Page 7972, left column, second column in Chames et al.) which can be used in therapy. In addition, when the purified Fab G8 was immobilized to a surface through its hexahistidine tag, the bound antibody was devoid of affinity sufficient to kill target cells *in vivo*. Moreover, the purified Fab-G8 antibody failed to detect HLA-A1 cells incubated with the MAGE-A1 peptide (see Chames et al., Page 7972, left column, third paragraph), thus could not be used for detecting or killing cells presenting the MHC-peptide complex.

In this regard, Andersen et al. (WO 97/02342) have not provided any further teachings which could advance the use of TCRL antibodies in human therapy in general and the treatment of virus infections, in particular.

The antibodies described in Andersen et al. (1997) and/or Reiter et al. (1997) are directed against mouse MHC-peptide complexes and not against human MHC-peptide complexes. As the mouse (e.g., GenBank Accession No. AAA53203) and human (e.g., GenBank Accession No. AAA76608) MHC molecules exhibit completely different chemical structures (with only 62.7 % of homology, see

sequence alignment, attached herewith), antibodies against mouse MHC-peptide complexes such as Fab 13.4 of Andersen et al. cannot be used for targeting and treating human cells. Thus the antibodies contemplated by Andersen et al. are no more than an expression of a desired result rather than actual conception and reduction to practice.

In view of the above remarks it is respectfully submitted that the teachings of Reiter et al. (1997) and Andersen et al. (WO 97/02342) cannot be used to render obvious the claimed invention. Withdrawal of the rejection is respectfully requested.

Reiter and Andersen in view of Matsushita

The Examiner has rejected claims 141-149 and 151-159 under 35 U.S.C. § 103(a) as being unpatentable over Reiter et al. and Andersen et al. as applied above, further in view of the teachings of Matsushita et al. (US 5,591,829). In addition, the Examiner states that claims 156 and 157 further require that the pathogen infecting the target cell is a retrovirus, particularly a human T-cell lymphotropic virus type I (HTLV-1). Specifically, the Examiner states that while the teachings of Reiter et al. and Andersen et al. suggest the use of the indicated antibody conjugates to kill pathogen infected cells in general, and demonstrate the efficacy of the conjugates to kill virus infected cells, they do not specifically teach or suggest embodiments wherein HTLV-1 infected cells are targeted. However, Matsushita et al. teach similar methods to those in Reiter et al. and Andersen et al. for the killing of retrovirally infected cells. The Examiner further states that while the reference uses antibodies targeting the pathogen antigen directly, instead of the MHC-antigen complex, from the teachings of Reiter et al. regarding the virus infected cells, it would have been apparent to those of ordinary skill in the art that the antibodies of Reiter et al. and Andersen et al. would be functional equivalent for the antibodies of Matsushita et al. The Examiner's rejections are respectfully traversed.

Relying on the above arguments it is Applicants' position that the claimed invention cannot be rendered obvious by the teachings of Reiter et al. and Andersen et al. even when combined with the teachings of Matsushita et al., who merely teach antibodies directed against pathogenic epitopes. Withdrawal of the rejection is respectfully requested.

Reiter and Andersen in view of Saito

The Examiner has rejected claims 141-149 and 151-160 under 35 U.S.C. § 103(a) as being unpatentable over Reiter et al. and Andersen et al. as applied above, further in view of the teachings of Saito et al. (J. Virol. 75: 1065-71). The Examiner further states that claim 160 requires that the antigen in the complex is a Tax protein polypeptide antigen. The Examiner states that Reiter et al. and Andersen et al. do not specifically teach or suggest embodiments wherein the antigens are HTLV-1 antigens, or Tax protein antigens, however, Saito et al. teach that, in certain HTLV-1 infected patients, cells comprising HLA-A2/Tax peptide complexes appear to be involved in the pathogenesis of the disease, and that from these teachings, those of ordinary skill in the art would have been motivated to kill these cells in the indicated subgroup of HTLV-1 infected patients. The Examiner states that those of ordinary skill in the art would have had a reasonable expectation of success in the use of such antibodies in view of the teachings of Saito et al. indicating that these cells were the cause of the pathogenesis in certain HTLV infections, and the demonstration and suggestion in Reiter et al. and Andersen et al. regarding the use of the antibodies to target MHC/peptide complex expressing cells. The Examiner's statements are respectfully traversed.

Relying on the above arguments it is Applicants' position that the claimed invention cannot be rendered obvious even when combined with the teachings of Saito et al., who merely teach the involvement of HLA-A2/Tax peptide complexes in certain HTLV-1 infected patients. Withdrawal of the rejection is respectfully requested.

Reiter and Andersen in view of Saito and Hoogenboom

The Examiner has rejected claims 141-160 under 35 U.S.C. § 103(a) as being obvious over Reiter et al., Andersen et al. and Saito et al. as applied to claims 141-149 and 151-160 above, further in view of Hoogenboom et al. (US 2003/0223994). The Examiner states that claim 150 reads on embodiments wherein the antibody used in the method comprises the sequence of SEQ ID NO:23. The Examiner states that because the antibody disclosed in Hoogenboom et al. performs the function of the antibody suggested by the combination of Saito et al. with the teachings of Reiter et al. and Andersen et al. it would have been obvious to those of ordinary skill in the art to use the antibody of Hoogenboom et al. in the methods suggested by the other references. The Examiner's statements are respectfully traversed.

Relying on the above arguments it is Applicants' position that the claimed invention cannot be rendered obvious by Andersen et al. and Reiter et al. even when combined with the teachings of Saito et al.

Furthermore, the Examiner's attention is drawn to US 2003/0223994 which has a common inventor with the subject application, Yoram Reiter. Attached is a declaration attesting that the antibodies directed against human MHC-peptide complexes disclosed in US 2003/0223994 were derived from conception of Yoram Reiter solely and therefore, this disclosure was derived from the inventor's work. See the attached declaration under 37 CFR 1.132 by the present inventor, Dr. Yoram Reiter stating that the subject matter claimed in claim 150 of the instant application is not an invention by "another". Accordingly, withdrawal of this rejection is respectfully requested.

In view of the above claim amendments, arguments, remarks and Declarations Applicants believe to have overcome the 35 U.S.C. § 103 rejections.

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Double Patenting

The Examiner has provisionally rejected claims 141-160 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-50 of copending Application No. 11/203,137.

In addition, the Examiner has provisionally rejected claims 141-160 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8, 11, of copending Application No. 11/629,194.

Applicants respectfully request that the provisional rejections be held in abeyance until such time as claims are determined to be allowable or issue in the copending applications.

In view of the above amendments, remarks and Declaration by the present inventor, it is respectfully submitted that claims 141-160, 196-211 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: July 24, 2007

Enclosures:

- Petition for Extension (3 Months)
- Additional Claims Transmittal Fee
- Declaration and CV of Inventor Yoram Reiter (derivation)
- Declaration and CV of Dr. Charles DeLisi
- Declaration and CV of Prof. Vincenzo Cerundolo;
- Alignment between the mouse and human MHC molecules
- **References**
- Weir AN., et al., Biochem Soc Trans. 2002 Aug;30(4):512-6, Abstract.
- Tamminen WL., et al., Eur. J. Immunol. 1987, 17:999-1006;
- Rubin B., et al., 1989, Res. Immunol. 140:67-74;
- Chames P., et al., PNAS, 2000, 97:7969-7974;